THE RELATIONS BETWEEN THE INTERSTITIAL GLAND OF THE TESTICLE, SEMINIFEROUS TUBULES AND THE SECONDARY SEXUAL CHARACTERS.[1]

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The following observations may prove of interest in the analysis of the relations between male gonads and secondary sexual characters.

While, as is often the case, an experiment of nature, unaided by experiments in the laboratory, is unable to give a definite answer to the questions which it raises, yet it would at present be impossible to duplicate at will in the laboratory an experiment such as we observed and it is, therefore, desirable that it should be recorded.

Our observations were as follows:

Guinea pig No. 1523 had been sent to our laboratory by an animal breeder as a female that had apparently been in heat, but in some respects behaved abnormally. The report of the breeder was as follows:

"The female through her actions gave every sign of being in heat; but upon examining her, she did not look to me as if she really was in heat. I had her with two other females and she would mount them just the same as a male guinea pig would do when in the act of copulation and she would also allow the other females to act in the same way. She would stand in this position, meanwhile expanding the vagina, which generally is a sure sign of their being in heat. I would say that she is with young; at least she should be pregnant, because she had been with a male for some time. Expect some young at any time."

The breeder made his observations July 8, 1917. On July 12, 1917, the animal, which weighed 615 grams, was prepared for operation. Under ether anesthesia lumbar incisions were made,

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in order to expose the ovaries. Typical ovaries were, however, not found. Instead, we encountered near the place where the ovaries usually are situated, but perhaps a little farther down, somewhat large and round, rather soft bodies, each about the size of a pea, surrounded by much fat tissue. On cutting through the center the color was found to be slightly yellowish-brown. From here some fibrous bands extended downward in the direction in which the uterine horns are usually situated. An organ that resembled the uterus was not found. The vagina was also lacking. Neither was a penis, vas deferens or a descended testicle visible.

The brownish red bodies as well as pieces of the fibrous bands were fixed in Zenker. Both of the bodies were completely cut into serial sections. Tissue from the places where the mammary glands are usually situated was also fixed and sectioned.

Microscopic examination:

1. The round bodies situated below the kidney were seen, microscopically, to consist of testicle tissue in which there was an extraordinarily marked development of interstitial gland. The testicle tubules were lined by one layer of epithelial cells, the outline of which was not very definite. Towards the center of the tubules they formed a network of fine fibrils; a sharply defined lumen therefore did not exist in the tubules. The cells had either a cuboidal or cylindrical form as far as their indefinite outline permitted of such a characterization. In some cases the whole protoplasm of the cell was drawn towards the center of the tubule in a tail-like structure. The nucleus was situated in the center of the cell and was very characteristic. It represented a clear vesicle in which one deep-staining large nucleolus was visible. Occasionally the nucleolus divided into two parts. In various places the tubules were lined with several cell rows. Sometimes the cytoplasm and the nucleus of one cell swelled, and such a cell encroached upon the territory of the neighboring cell, lying more towards the center of the tubule, pressing against it; and thus one cell surrounded, crescent like, the neighboring cell. Occasionally some cells degenerated, the nucleolus persisting longest, while the rest of the nucleus had already disappeared. Mitoses were seen quite frequently in these tubule cells and monasters as well as diasters

were found. The tubules were enveloped by a circular layer of flat connective tissue cells, which were drawn out into long fibers with flat nuclei. Each tubule was surrounded by several, usually two to five, layers of interstitial cells. Each tubule with the surrounding concentrically arranged interstitial cells formed a group which was often quite sharply separated from neighboring similar groups through lymph vessels or lymph-spaces and blood vessels and accompanying connective tissue strands. In certain places larger blood vessels accompanied by lymph vessels were found in the tissue. Blood capillaries were numerous in certain places. Occasionally a tubule was found adjoining the connective tissue directly, without being separated from the latter by interstitial cells. The character of the interstitial cells varied somewhat in different parts of the organ. Usually they were large polygonal, partly rounded off or oval cells with a large vesicular nucleus, in which several small nucleoli were generally seen, instead of the one clear nucleus which was so characteristic of the tubule cells. The nucleus in the interstitial cell was not so light and transparent as in the tubule cell. The sizes of the interstitial cells varied. The cytoplasm became finely vacuolar, at first in the periphery. In the center there was still a solid material staining red with eosin. Later the whole cytoplasm became finely vacuolar. This vacuolization was usually accompanied by a considerable increase in size of the cells. In some cases the vacuoles enlarged still more, the walls separating neighboring vacuoles disappeared and irregular cavities became visible in the cells. In those cases the nucleus became irregular and shrank, and when this last stage had been reached, the cell was evidently degenerating. Many finely vacuolar enlarged cells appeared otherwise normal and viable. These finely vacuolar, swollen cells occurred especially around the lymph vessels, or perhaps also around certain blood vessels. We must assume that substances reaching the cells from the circulation were deposited within the cells and caused the vacuolization, the nearness to the source of this substance determining the frequency and intensity with which these changes took place. Under the same conditions the accompanying fibrous tissue became edematous. Apparently the vacuolization of the interstitial cells and the edema-

tous state of the stroma are analogous phenomena. We were only rarely able to find mitoses in the interstitial cells. In this respect the latter differed from the tubule cells in which mitoses were quite frequent. There could be found at one end of each testicle a system of branching epithelial ducts, with a narrow lumen. They were lined by a layer of small and densely packed, usually cuboidal or flat epithelial cells, with nuclei which filled the greater part of the cells. In these cells either one or several nucleoli were found. If one nucleolus was present the nucleus resembled that of the tubule cells, except that it was smaller. At other places the lining cells and nucleus were low cylindrical. In the lumen of these ducts not infrequently some invaginations of the epithelium were found. On the one side the ducts formed a union with the tubule of the testicle. Between the two we found transitional structures consisting in part of tubular and in part of duct epithelium. At the other end the ducts entered the fat tissue which surrounded the testicle and made connection with some larger ducts. One change that took place in a number of tubules needs special mention: A few or many, at some places even the majority of the tubule cells underwent certain changes which made them very similar to interstitial cells. They enlarged, became polygonal or somewhat round, and their cytoplasm stained more strongly with eosin. The cytoplasm became finely vacuolar, at first the periphery and later the greater part of the cell undergoing this change. At the same time the nucleoli divided into several particles which were dispersed in the nucleus. The nucleus became a round vesicle which had lost the transparency so characteristic of the nucleus of the tubule cells. Accompanying this change the layer of flat connective tissue cells which separated tubules and interstitial cells disappeared and at various places interstitial cells adjoined directly the tubule cells, both kinds having become very similar. Such changes seemed to be frequent especially in places where the interstitial cells were swollen and had become finely vacuolar. Three interpretations of this condition suggest themselves:

1. As a result of their enlargement the interstitial cells push into the tubules, and thus the appearance within the tubules of typical tubule cells adjoining directly cells resembling interstitial

cells might be explained. At the same time the enlarged interstitial cells exerted a pressure on the tubule cells which made them crowd closer together than usual. This interpretation is not admissible, because the cells within the tubule began to swell at a time when the connective tissue layer separating tubule and interstitial tissue was not yet broken through. At first the enlarging cells still possessed the nucleus characteristic of the tubule cells and only gradually the character of the nucleus changed concomitantly with the later stages of the transformation.

2. It might be assumed that an actual transformation of tubule tissue into interstitial tissue took place, and that the gland-like interstitial tissue was merely further differentiated tubular gland tissue. Many pictures seemed to suggest such an interpretation. However, the fact that in many other places, especially where the interstitial cells were still solid and smaller, and, therefore, younger, the line of demarkation between tubule and interstitial tissue throughout was very sharp made, after all, this interpretation improbable. Furthermore, it would be contradicted by what is known of the origin of the interstitial cells.

3. It is most probable that the same factors which produce the changes in the interstitial cells, at the same time called forth similar changes in the tubule cells. Probably certain substances furnished by the lymph or blood vessels were simultaneously responsible for both sets of changes. In favor of this interpretation might be cited the fact that we did not usually find in the tubules that extreme vacuolization, which was present in some of the interstitial cells. We are, therefore, inclined to adopt the third interpretation.

The round bodies which we found near the place where normally the ovaries are situated therefore represent undescended testicles. There is a system of ducts leading from the testicle tubules to the surrounding fat tissue. The tubules are relatively simple structures in which spermatogenesis does not take place. The epithelium lining them corresponds to the sustentacular cells of the normal testis. There is present an extremely marked development of the interstitial cells. The structure of this testicle differs, therefore, markedly from the normal testicle of the

guinea pig which consists principally of tubules with several layers of epithelium which are in the process of spermatogenesis. Between these tubules there is very little stroma with blood vessels and a very small number of polygonal cells.

Sections through the tissue, taken from the place where normally the uterus is situated, show fibrillar connective tissue in which are situated nests composed of rather large polygonal, cylindrical or ellipitical cells, the protoplasm of which stains well with eosin. The nuclei of these cells are round vesicle with chromatic particles distributed rather diffusely. These cells form the matrix of the neighboring fibrillar connective tissue. Through rarefaction of the cytoplasm and through a condensation, backing together of the nuclear chromatin these cells are transformed into the surrounding connective tissue. We also studied in microscopic sections the fat tissue which filled the space between the undescended testicle and the kidney, without finding any trace of further testicular or of ovarian tissue.

Mammary Gland.—The nipples of the guinea pig were distinct and we cut out pieces from the tissue where normally the mammary gland is situated. In the male a few scattered ducts lined by epithelium in which mitoses do not usually occur represent the mammary gland.[1] In our case, a very much furthergoing development of the mammary gland was found on microscopical examination. Sections through one of the two mammary glands showed solid tissue consisting of a large number of lobules of mammary gland tissue, joined together by thin strands of fibrous tissue. The whole gland was surrounded by fat. Each lobule consisted of acini lined by cuboidal epithelium of medium size. The nuclei were vesicular and relatively large. The lumen of the acini varied in size and often contained some colloid material or desquamated cells. Occasionally an acinus cell was found to be vacuolar. In the stroma between the acini there were numerous small connective tissue cells. At some places, where the interstices between the acini were somewhat wider and the stroma was slightly edematous, polynuclear leucocytes staining deeply with eosin were found. The largest ducts were

[1] In the ducts of the mammary gland of a young male guinea pig, about 30 days old, we encountered however one mitosis.

as usual surrounded by denser fibrous tissue. At one pole of the gland a system of ducts and acini lined by higher and larger epithelium extended into the surrounding fat tissue. The lumen of these ducts and acini was wider. Mitoses could not be seen in the mammary gland. The mammary gland of the other side, which was also surrounded by fat, was smaller, at least the amount of gland tissue found on sections, which had been through different parts of the piece, was less; but it still surpassed considerably that found in normal animals. Furthermore, the acini were composed of high cylindrical cells, surrounding a rather large lumen. There were a few desquamated cells in the gland lumina, the acini being arranged around the larger ducts. Here and there mitoses were seen in the acini. The stroma between the acini was loose in texture and contained a number of fibroblasts.

Discussion.—The following are the chief points of interest in these observations:

1. We have in this case apparently to deal with an undescended testicle in an adult guinea pig. Such testicles have been observed in man and several species of animal, especially in the horse and pig. This case is an example of the same condition in the rodentia. Common to all cases which have been so far described is an imperfect development of the seminiferous tubules and a hypertrophy or a hyperplasia of the interstitial cells of the testicle. As to the literature concerning such cases we may refer especially to Bouin and Ancel (1) Tandler and Grosz (2), and Whitehead (3). Both of the features we mentioned are present in a marked degree in our case. Spermatogonia are completely absent; the tubules consist entirely of Sertoli cells. The retention of the testicle acted in a way comparable to the ligation of the vas deferens which brings about similar results which are, however, usually not quite so far going. In addition, it is very probable that the condition which prevented the normal descent of the testicle was directly responsible for the lack of development of spermatogonia. As to the overdevelopment of the interstitial gland, in those cases, we may conclude that it stands in some causal relation and is subsequent to the underdevelopment of the seminiferous tubules. In various other conditions in which atrophy

or underdevelopment of the tubules has been observed, or produced experimentally (ligation of vas deferens, Roentgen ray injury of the testicle (4) (5) and certain diseases) a hypertrophy or a hyperplastic condition of the interstitial gland has been noted. Herxheimer and Hoffman (5) suggest that this hyperplasia is comparable to the substitutive growth of connective tissue which takes place whenever parenchymatous elements are destroyed. This explanation, however, does not seem to take into account the principal variations which have been observed in the condition of the interstitial gland. Bouin and Ancel (1) have shown that in the horse the interstitial gland is present in the fetus; it degenerates in the immature animal and begins anew to develop at the time of puberty. In the sexually mature animal there seems to exist a certain antagonism between the activity of the seminiferous tubules and the interstitial gland. The interstitial gland becomes hyperplastic in cases in which the tubules decrease in activity and vice versa. Under the conditions of tubular atrophy or degeneration which we named above the interstitial gland hypertrophies, and according to Tandler and Grosz in the mole, in which sexual activity follows a yearly cycle, the interstitial gland shows the greatest development at a time when the seminiferous tubules are least active. In hibernating animals the interstitial gland decreases at the period of general metabolic inactivity (von Hansemann); similarly in cases of very pronounced general undernourishment, or of very marked degenerative processes in the testicle the interstitial gland suffers and may disappear. Some observations indicate, furthermore, that under certain conditions extirpation of one testicle may lead to a hypertrophy of the interstitial gland in the second one. All these facts can evidently not be explained otherwise than by assuming that there are several factors active and that chemical and not merely mechanical substitutive factors play a rôle in the regulation of the growth of the interstitial gland. It seems to be a general function of gland and other epithelial cells to stimulate through their activity the surrounding stroma. We have described such an occurrence especially in connection with the cyclic growth of the mammary gland, but it seems to be a phenomenon of general significance. In a similar way we may as-

sume that growth processes in the seminiferous tubules stimulate the activity of the connective tissue cells and those specialized connective tissue cells which have the potentiality of becoming transformed into interstitial gland. This would explain the development of the interstitial gland during embryonic development and at the time of puberty. We might designate this as the concomitant growth of the interstitial gland. In order to explain the second kind of growth in the interstitial gland, which we might call the "alternative growth," we must assume that in a certain way the activity of the sexually active seminiferous tubules exerts an inhibiting effect on the growth of the interstitial gland and that a diminution of this inhibiting effect leads to the "alternative" growth of the interstitial gland. An analogous condition is found in the rabbit ovary in which the atresia of certain follicles leads to a secondary gland-like development of the theca interna. How far such an equilibrized condition is maintained through chemical, how far through finely adjusted mechanical factors, we do not know at present. However, in the somewhat analogous case of the transformation of the connective tissue cells of the uterine mucosa into decidua, we have analyzed the underlying factors experimentally and found that a combination of specific chemical and mechanical factors, which latter are likewise to a certain extent specific, is responsible for this change (6).

In addition, the interstitial cells of the testicle are accessible to that chemical stimulation which is implied in compensatory hypertrophy and they are furthermore affected by lack of common foodstuffs.

2. The specific effects exerted by the interstitial cells have been ascribed by Bouin and Ancel to certain products formed within the cells which microchemically behave like fats or lipoids. We found, in our case, reasons for assuming that drop-like substances were furnished the interstitial cells from the surrounding lymphatics and perhaps also from the blood capillaries. How far the substances taken up from the circulation and perhaps modified within the cells are identical with the substances described by Bouin and Ancel and Whitehead, we cannot at present decide.

3. Various writers, especially Bouin and Ancel, concluded that the interstitial cells of the testicle are responsible for the development of sexual desire in the male. Our observations seem to confirm this view. The complete absence of spermatogonia in the tubules, together with the marked development of the interstitial gland was accompanied by the presence of marked manifestations of sexual instinct.

4. Bouin and Ancel, Steinach (7, 8) and Tandler and Grosz not only ascribe to the interstitial gland the function to cause chemically those nervous changes which find expression as sexual desire, but the additional task of enhancing the development of the male sexual characters, of allowing the full development of prostate, penis, seminal vesicle, and of suppressing the development of the female secondary characters. Our observations apparently contradict these conclusions. In our case, the very marked development of the interstitial gland was accompanied by the absence of penis, seminal vesicles (and presumably of prostate), and on the other hand was associated with a very marked development of the mammary gland. The latter resembled a proliferating breast, a "proliferating gland" such as Dr. Hesselberg and the writer found it in certain stages of the sexual cycle in the female guinea pig (9). Our observations prove that the presence of a very strongly developed interstitial gland is perfectly compatible with the existence of certain female, and with the absence of certain male secondary sexual characters. A priori two interpretations of this fact are possible:

(*a*) The interstitial gland of the testicle has not a specific function in the sense assumed especially by Bouin and Ancel and Steinach. (*b*) The interstitial gland is specifically "male enhancing" in its function, but the end effect does not only depend upon this specific action of the interstitial gland, but also, and primarily so, on the system on which it acts. We have reason for assuming that in a certain respect an individual can be compared to a more or less sensitive balance in his or her sexual potentialities and that different individuals of a certain species differ in the resting point of their sexual equilibrium (10, 11, 12, 13, 14). Without the interference of hormones which are produced by the gonads, the point of equilibrium in some individuals

would be neutral; in others it would be deviating more or less in the direction toward the male; in still others toward the female side. On the whole the male would usually deviate to the male and females to the female side. However, differences exist in this respect in different classes and species of animals and also in individuals of the same species. There are, furthermore, differences in the relative degree of stability of this point of equilibrium. In insects it is apparently very stable and little or not at all influenced by hormones of gonads; in mammals the equilibrium is labile and readily influenced by hormones of the gonads. In mammals, the male hormones can be compared to weights added to the male side of the scales and female hormones influence the scales in the opposite direction. It seems probable that in our case we had to deal with an individual with imperfect male gonads which represented a system with a very slight tendency towards the male side and with a relatively strong tendency toward the female side. In such an individual with tendency toward female secondary sexual characters even a strong male hormone is not able to prevent the growth of the mammary gland, and this female tendency is probably in some way connected with the suppression of male secondary characters during embryonic development, and perhaps also directly or indirectly with the failure of the testicle to descend to its proper place and develop perfectly. In such a relatively stable system tending toward femaleness in its secondary characters, even a specific male hormone, such as is supplied by the interstitial gland of the testicle, has little chance to become effective. Whether, under certain conditions, the hormone given off by the interstitial gland of the testicle might in addition be able to promote growth of the mammary gland, cannot be decided on the strength of the evidence which we have at present.

Summary.

1. It is shown that in a guinea pig with undescended testicle, in which spermatogonia were lacking, and the interstitial gland was hypertrophic, sexual desire was strongly developed.

2. An attempt is made to analyze the various factors that determine the growth of the interstitial gland in the testicle.

3. It is shown that, notwithstanding the presence of a hypertrophic interstitial gland, there was an absence of male secondary sexual characters and that the mammary gland had a female character. A provisional interpretation of these facts is given on the basis of our present knowledge of sex determination.

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Additional Note

The foregoing paper was written without the knowledge of two quite recent, very important publications by F. R. Lillie and C. L. Chapin, which may have some bearing on our observations, and which it will therefore be necessary to briefly discuss from

[1] F. R. Lillie, *Journal Exper. Zoölogy*, 1917, XXIII., 371. C. L. Chapin, *ibid.* 453. I am much indebted to Prof. Lillie for calling my attention to these papers,

this point of view. In the first of these two papers Lillie gives a detailed account of the anatomy of the internal and external genital organs in freemartins in various stages of embryonic development and of his interpretation of the cause of the abnormalities and in the second paper Chapin describes the microscopical findings in these cases. It follows from Lillie's observations and analysis that the sterile freemartin represents an individual which was originally a female, but in which under the influence of hormones carried into her circulation from the chorionic vessels of a male twin, the female characteristics were more or less suppressed and male characters acquired. This not only applies to the secondary sexual characters, but even to the structure of the gonads. As Chapin has shown, the development of the ovarian cortex and of ovarian follicles is more or less interfered with or may be altogether suppressed, and the medullary sex cords develop often in a way similar to the seminiferous tubules, although spermatocytes or spermatozoa to not seem to be produced. The development of the Müllerian ducts is likewise interfered with and seminal vesicles may develop instead. The external genitalia and the mammary gland are least affected by the male forming substances, which according to Lillie originated in the testicle of the male twin and were from here transmitted to the female twin; these latter organs remain usually female in character.

These important findings may have some bearing on the interpretation of our observation. There exist undoubtedly marked similarities between the condition found in the freemartins and in the condition of the genital organs of the guinea pig which we examined. However, while Lillie and Chapin examined embryological material, we have to deal with an adult animal.[1] In our case we observed a gonad which shows the characteristics found in testicles under various pathological conditions. Similar changes have been produced in testicles experimentally under the influence of Roentgen rays. The tubules, the character of the cells composing them and particularly of the nuclei closely resemble structures which we found after transplantation of

[1] Microscopic sections through the gonads of an older freemartin from the material of Dr. Lillie show a great similarity with our sections through the gonads of the guinea pig.

testicle and epididymis in the guinea pig. The interstitial cells are developed to an extraordinary extent. The organs were cut in complete serial sections and no trace of ovarian structure was found. From the descriptions given by Miss Chapin, I should judge that a similar condition has not been observed in the fetal gonads of the freemartins. In the guinea pig, uterus and vagina as well as vas deferens, seminal vesicles and penis were absent. While I was unable to find a description of the histology of the mammary gland in freemartins, we observed in our case a typical female mammary gland with the added peculiarity that the mammary glands of both sides were unequal.

The question arises, whether the guinea pig which we observed was an analogue to the freemartin in cattle. Was this animal originally the twin sister of a brother, under whose influence the observed deficiencies were produced? While we cannot definitely exclude such a possibility we must consider the fact that neither ourselves nor anyone else has so far observed twins with a common chorion and deficiencies in the development of the sexual organs in rodents. Lillie himself points out the great improbability of such an occurrence in animals in which the ova enter the uterine wall at an early date and in which the uterine horns are separated. On the other hand, we accidentally observed in several cases absence of one uterine horn in guinea pigs. Malformations of the sexual organs do therefore occur. It is very probable that similar malformations may be due to different interferences in the embryo, just as we know that cyclopic conditions of the eye can be produced in different ways. We interpreted in our paper the conditions which we found in the guinea pig as consisting essentially in the presence of an abnormal, incompletely developed male gonad in which generative cells are absent, and in which the interstitial cells show an unusually pronounced development. This maleness of the gonad and especially the marked development of an interstitial gland is associated with deficiencies in the formation of the efferent genital ducts and with a female mammary gland. We interpreted this unusual condition as due to the original female constitution in the animal, to the tendencies toward femaleness which prevented the male interstitial cells from exerting their specific influences

on the mammary gland, If this guinea pig should represent an analogue to the freemartin in cattle, we would have to assume that the male characteristics of the gonad were produced in an original female through the influence of the testicular substance of the male brother. While such an origin has been made possible through the findings of Lillie, the essential point is that, whatever the origin of this condition, we have every reason to consider the gonad which we described as male.

It is the complete examination of the gonads in serial sections which makes it possible for us to exclude the presence of ovarian structures in this animal and to prove the similarity of the organs with the testicles found under certain experimental and natural pathological conditions. There is no reason for assuming that the gonads in our case represented really ovarian tissue. We have examined many hundred of ovaries of guinea pigs of various ages and have never been able to detect in the ovaries of guinea pigs structures resembling the interstitial gland of the testicle, while on the other hand such structures are strongly developed in testicles which have been retained in the abdominal cavity.

The findings of Lillie and Chapin suggest very strongly, and I take this also to be the interpretation of Lillie, that even in the freemartin the gonad which originally was destined to become female, assumes at least in part true male characters. If this were not so, it would be difficult to explain why seminal vesicles could develop in a freemartin. We should expect that the autogenous ovarian substances would prevent the heterogenous testicular substances from exerting such an influence on the secondary sexual organs of the female twin.

We found in our case a marked development of sexual instinct associated with the absence of generative cells and with a very marked development of the interstitial tissue. Now, as we have pointed out in previous papers, it is improbable that in the guinea pig the interstitial gland is responsible for the manifestation of sexual desire in the female.[1]

[1] Loeb, Leo, *Zentralblatt f. Physiologie*, 1911, XXV., No. 9, and Loeb, Leo, "The Relation of the Ovary to the Uterus and Mammary Gland from the Experimental Aspect," *Surgery, Gynecology and Obstetrics*, 1917, XXV., p. 300. (A review of the literature concerning this and other aspects of the mechanism of the sexual cycle.) In accordance with the most widely accepted view we assumed in our

Typical interstitial cells are absent in the normal ovary of the guinea pig. If we should assume the gonads in this guinea pig to be female our own observation would constitute a decisive proof that also in the female guinea pig the interstitial cells produce the substance which is responsible for the sexual desire—a conclusion which, however, as we stated above, would be contradictory to other facts which we established previously.

The case which we described may be compared to a single equation communicated by nature, in which two variables are present. While one equation is not sufficient to determine the unknown factors in such a case, the variables have at least been carefully defined in our case. We may hope that later a second equation will be found which will permit defining all the variables. We thought it therefore of interest that these observations should be published.

discussion that it is the so-called interstitial gland of the testicle which is responsible for the development of the secondary sexual characters and of sexual desire in the male. We wish, however, to emphasize the fact that in our case epithelial elements were present in the testicle in addition to the interstitial gland and apriori we cannot exclude the possibility that they and not the interstitial gland are the causative agency in determining sexual phenomena. We are likewise not certain that this can be excluded in those experimental and pathological conditions in which the changes were attributed to the interstitial gland. However we are not directly concerned with this question and we are not in a position to contribute definite data which would favor or contradict this view. We wish, however, to reiterate the fact that on various occasions we made observations which do not seem to accord with the assumption that in the ovary the so-called interstitial gland initiates heat.